Original Article

TRANSLATIONAL&PRACTICAL MEDICINE

DOI: 10.51271/JTPM-0048

J Transl Pract Med. 2023;2(3):89-94

Investigation of brucellosis cases in and around Yozgat province

Duygu Felek[1], Canberk Çınar[2]

[1]Department of Internal Medicine, Sorgun State Hospital, Yozgat, Turkey
[2]Department of Medical Microbiology, Sorgun State Hospital, Yozgat, Turkey

Cite this article as: Felek D, Çınar C. Investigation of brucellosis cases in and around Yozgat province. *J Transl Pract Med.* 2023;2(3):89-94.

Received: 18/08/2023 ◆ **Accepted**: 21/09/2023 ◆ **Published**: 31/12/2023

ABSTRACT

Aims: Brucellosis causes a zoonotic infectious disease that is very common in our country as well as around the whole world. Infected individuals most frequently present with nonspecific symptoms such as fever, chills, malaise, and generalized body pain. Therefore, it is very difficult to diagnose. When diagnosis and treatment are delayed, it causes serious complications. It can cause pictures with high mortality due to endocarditis and morbidities such as epididymoorchitis, hepatitis, neurobrucellosis, and pancytopenia. The first approach to treatment is rest. Antibiotics with intracellular bactericidal action should be used in combination due to resistance development.

Methods: 136 individuals with serum titers who were diagnosed with brucellosis by serological tests and who applied to our hospital between 2017-2022 were included in the study. The patient files were analyzed to evaluate the complaints of these individuals, their *Brucella* ELISA titers, serum aspartate aminotransferase (AST), alanine aminotranspherase (ALT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH) values, if any, at the time of diagnosis, the treatments they received, and the response to the treatment.

Results: The first complaints of 136 patients who were diagnosed with brucellosis by serological tests were the most common; joint pain was present in 48 (35.29%), widespread body pain in 26 (19.11%), and fever in 18 (13.23%). Sacroiliitis in 5 (3.67%), gonarthrosis in 4 (2.94%), bursitis in 4 (2.94%), discitis in 3 (2.2), and psoriasis in 1 of the patients' abscess (0.73%) was detected, respectively. R=0.28 in the same direction between the first titers recognized by the patients and ALT; the same direction between titer and LDH R=0.30; the same ratio between titer and CRP is R=0.45; and there is a correlation coefficient of R=0.26 between titer and sediment in the same direction. It is important to take these correlation coefficients statistically ($p<0.05$). Accordingly, these values also change when it titrates. But it is weakened weights as a measure of relationship.

Conclusion: Although fever comes to mind first in brucellosis, it was observed that the first complaint of individuals in our study was complicated surgery, and fever ranked third. For this reason, Brucellosis should be approached with suspicion, since it is endemic in individuals presenting with non-specific complaints. It is widely present between serum titer and ESR, and C-reactive protein as markers of inflammation. In individuals with high vibration and inflammation markers, controlled caution should be exercised. Even treatment times can be changed.

Keywords: Brucellosis, symptoms, complications, diagnosis

INTRODUCTION

Brucella is a small, gram-negative coccobacillus. It causes a zoonotic infectious disease that is very common in our country as well as all over the world. The disease is transmitted by the consumption of body fluids, waste materials, poorly cooked meat, and milk from infected animals. Although rare, there are literature data on blood transfusion from infected donors, neonatal and sexual transmission. In studies conducted in 19-23 rural areas, infected unpasteurized milk was observed as the most common transmission. Individuals in close contact with animals, such as veterinarians, slaughterhouse workers, butchers, dairy operators, and laboratory workers, are at risk.[1-3] The incubation period of brucellosis is 7-21 days. The disease produces IgM and IgG positivity approximately 2-3 weeks after contact with infected material. IgG remains positive in the blood for a long time. The *Brucella* serum agglutination test (SAT) or Wright test is used in the diagnosis. However, the Rose Bengal screening test is also used to rapidly diagnose brucellosis.[4,5]

Infected individuals most commonly present with non-specific symptoms, such as fever, chills, malaise,

Corresponding Author: Duygu Felek, d.kocamemik@gmail.com

This work is licensed under a Creative Commons Attribution 4.0 International License.

generalized body pain, and headaches. Since it causes nonspecific symptoms, it is very difficult to diagnose. Brucellosis is characterized by a corrugated (fluctuating) fever, which has a specific definition of fever and continues for months with a fluctuating course.[6] While the success of treatment is high when diagnosed early, it can cause serious complications when diagnosis and treatment are delayed. It may progress with relapse and reinfection. Epididymoorchitis, endocarditis, hepatitis, neurobrucellosis, and pancytopenia may cause high mortality.[7,8]

The first approach to treatment is rest. Intracellular bactericidal antibiotics should be used. Tetracycline, streptomycin, rifampicin, and doxycycline are the most commonly used antibiotics. Doxycycline (200 mg/day) and rifampicin (600-900 mg/day) in combination for at least 6 weeks is the most commonly used treatment protocol. Treatment with single antibiotics leads to bacterial resistance and treatment failure.[9-14]

As the population is getting older and obesity is increasing, osteoarthrosis and muscle-joint problems are on the rise and may be confused with diseases involving the joints such as brucellosis, and sometimes the diagnosis of brucellosis may be delayed. In addition, almost every condition that causes fever can lead to muscle-joint pain, which makes it difficult to think of brucellosis at first.

Brucellosis was first diagnosed in our country in 1905 by Akalın et al.[11] in a military hospital. Subsequently, many studies have been conducted on brucellosis until today; however, in the new century, brucellosis cases have still not been prevented with both informative studies and measures taken.[12,13] Although brucellosis has been eradicated or controlled in many countries today, it is still common in some regions of our country and is included in the group of notifiable diseases. Our study shows that in the last five years, brucellosis cases have still been encountered in and around Yozgat province in the Central Anatolia Region, which is characterized as the endemic region of Turkey. Therefore, active screening and public awareness programs are needed.[14]

The most important point in the diagnosis of a disease is that the disease comes to mind. By examining the brucellosis cases in and around Yozgat Province, where livestock farming is common and brucellosis is therefore frequently seen, we aimed to bring the data from a region of our country to the literature, to remind people of the disease by sharing our data and experiences with our colleagues, and to contribute to their clinical practice.

METHODS

Ethics

Ethics committee approval was granted by Yozgat Bozok University Clinical Researches Ethics Committee (Date: 10.11.2022, Decision No: 2017-KAEK-189_2022.11.10_06. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Institutional approval was obtained.

Design

The study was planned as a retrospective cross-sectional study.

Patients

The data were collected after approval from the local ethics committee.

Inclusion Criteria

The files of 136 individuals who were admitted to our hospital between 2017 and 2022 and were serologically positive for brucella were reviewed.

Exclusion Criteria

Patients with missing data in their files were excluded.

Methods

Age, gender, presenting complaints and serum ALT, AST, lactate dehydrogenase (LDH), CRP, erythrocyte sedimentation rate, and brucella tube agglutination titer values were recorded. Treatment was received, and treatment response assessment markers were recorded. Treatment non-compliant and lost to follow-up patients were excluded from the study.

Statistical Analysis

The SPSS (Statistical Package for the Social Sciences) 22.0 program was used for statistical analysis of the data. Categorical measurements were summarized as number and percentage, and continuous measurements as mean and standard deviation (median and min-max where necessary). The Spearman rank correlation coefficient was used for analysis.

RESULTS

The minimum and maximum ages of the 138 individuals included in the study were 17 and 80 years, respectively, with a mean age of 43.99±14.63 and a median age of 45 years. Of these individuals, 92 (67.6%) were male and 44 (32.4%) were female. The initial presenting complaints were joint pain (40 knees, 8 hips) in 48 (35.29%), generalized body pain in 26 (19.11%), fever in 18 (13.23%), headache in 11, night sweats in 12 (5

Table 1. Data of biochemistry values of individuals with brucellosis						
	N	Minimum	Maximum	Mean	Medyan	Std. deviation
ALT (U/L)	134	6.00	253.00	44.9328	34.50	43.50615
AST (U/L)	129	11.00	210.00	39.2326	32.50	31.27337
LDH (U/L)	78	2.44	874.00	262.7086	234.50	136.10563
CRP (mg/L)	133	1.04	139.70	24.0995	15.55	27.25452
ESH (mm/hr)	128	1.00	84.00	28.8281	27.50	19.37411

Abbreviations: ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

accompanied by weight loss), low back pain in 10, nausea in 5 (3.67%), testicular pain in 5 (3.67%), and palpitations in 1 (0.73%). Three individuals were asymptomatic, and their first-degree relatives were found positive during screening.

Complications included epididymoorchitis in 5 (3.67%), sacroiliitis in 5 (3.67%), gonarthrosis in 4 (2.94%), bursitis in 4 (2.94%), discitis in 3 (2.2%), and pseudo-abscess in 1 (0.73%). One of the patients with neurobrucellosis and one with endocarditis continued their treatment at the upper center. One individual was receiving standard tetracycline rifampicin treatment but did not comply with the treatment due to irregular drug use and treatment success could not be achieved, and streptomycin was added to the treatment.

In the laboratory records, the mean ALT was 44.93±43.50 (ALT normal limits: 0-41 U/L) and the mean AST was 39.23±31.27 (AST normal limits: 0-41 U/L) at the time of the brucellosis diagnosis. In individuals with high ALT values, the mean ALT value was 99.5 U/L and the AST value was 84.92 U/L. The ALT value was more than three times the upper reference limit in 13 patients, while the AST value was more than three times the upper reference limit in 8 patients. C-reactive protein (CRP) was in the normal range at the time of diagnosis in 27 patients, between 50 and 100 mg/L in 9 patients, and 100 mg/L in 3 patients. ESR was in the normal range of 38 individuals, with a maximum value as high as 84. The mean CRP was 24.09±27.25 and the mean erythrocyte sedimentation rate (ESR) was 28.82±19.37 (Table 1).

The correlation coefficient between the initial agglutination titers and ALT was R=0.28 in the same direction; between the titer and LDH was R=0.30 in the same direction; between the titer and CRP was R=0.45 in the same direction; and between the titer and the ESR was R=0.26 in the same direction. This coefficient of association was statistically significant ($p<0.05$). Accordingly, when titer increases, these values also increase. However, they are weak correlations as a measure of association. No significant difference was found between titer and AST ($p>0.05$) (Table 2).

Table 2. Association of Brucella ELISA titers with biochemistry data					
Titer	ALT	AST	LDH	CRP	ESH
R	.141	.28	.30	.45	.26
P	.102	.001	.001*	.001*	.002*
n (individual)	136	136	136	136	136

Abbreviations: R: correlation coefficient, $p<0.05$ significant
ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, ESR; Erythrocyte sedimentation rate
(It is calculated as confidence interval R 95%, ALT 0.12-0.16, AST 0.22-0.30, LDH 0.27-0.33, CRP 0.39-0.51, ESH 0.24-0.28)

Distribution of *Brucell*a ELISA titer results among individuals in Table 3.

Table 3. Distribution of *Brucella* ELISA titer results among individuals		
Titer	n (Number of individuals)	Percentage (%)
40	2	1.5
80	8	5.9
160	17	12.5
320	27	19.9
640	22	16.2
1240	23	16.9
2560	11	8.1
5120	18	13.2
10240 and above	8	5.9
Total	136	100.0

DISCUSSION

The mean age of the 138 cases we reached within the scope of the study was 43.99 years, and 67.6% of the cases were male and 32.4% were female. In a study conducted by Köse et al.[15] in Western Anatolia, which is socioeconomically ahead of our region, 72 cases were retrospectively analyzed, and the mean age of the cases was found to be 44.8 years, similar to the figure we reached in this study. However, contrary to our findings, the majority of the patients in this study were women,

with a rate of 55.6%. We hypothesize that this difference is due to migration-based gender-based demographic segregation between regions and the relative lag of women in Central Anatolia in terms of participation in socioeconomic activities. Another hypothesis, which we hope is not true, is that women in our study region are behind in accessing health services for various reasons, and therefore cases are not detected and treated.

In the study conducted by Tohme et al.[16], the most common presenting complaints were fever, sweating, malaise, and pain. When we think of brucellosis, fever comes to mind first, but in the study conducted by Saçar et al.[17] the most common symptom was arthralgia, followed by fever. In our study, the most common presenting complaint was arthralgia, and fever was the third most common symptom. In a study by Sahin et al.[18] including 83 individuals, epididymoorchitis was the most common complication with 3.6%. In our study, epididymoorchitis was one of the most common complications with a rate of 3.67%, the same rate as in the study of Sahin et al.[19]. However, sacroiliitis was the other most common complication, with the same rate as epididymoorchitis.

CRP was within the normal range at the time of diagnosis in 27 patients (20.3%), between 50 and 100 in 9 patients (6.7%), and above 100 in 3 patients (2.25%). In 2018, a study conducted in Bosnia and Herzegovina examined brucellosis cases and analyzed CRP data from 19 of the cases. CRP values were below 5 mg/ml in 6 cases (31.6%), 50-100 mg/ml in 2 cases (10.5%), and above 100 mg/ml in 2 cases (10.5%). Although there is a significant difference between the groups when these figures are compared, it is seen in both studies that the CRP value was negative in the majority of the patients, and the number of cases decreased as CRP increased.[18] In terms of ESR, another acute phase reactant that is routinely used and attributed importance, 38 (29.68%) of the 128 patients in whom we had ESR values resulted in ESR within the normal range. In the Bosnia and Herzegovina study in which we compared CRP data above, ESR was found to be below 25 mm/hour in 12 of 19 patients (63.2%). Based on these data, it can be said that the importance of CRP and ESR in brucellosis should not be underestimated, but their negativity should be approached with caution, especially in the presence of clinical suspicion.

The relationship between brucella titer and disease has been studied.[19-22] In a study by Demir et al.[20] evaluating the relationship between agglutination and CRP as an acute phase reactant, 121 individuals with serum tube agglutination of 1/160 and above were included among 4041 patient sera sent with suspicion of brucellosis; the same directional relationship was found between titer and CRP. It was thought that CRP could be used in the diagnosis and follow-up of brucellosis. In our study, similar to many studies, a positive correlation was found between CRP and ESR values, which can be evaluated with disease severity and brucella titer.

The mean ALT in our patients was 44 (ALT: N: 0-41 U/L), and the number of patients with ALT values higher than three times the upper reference limit was 13 (9.7%). In a previous study conducted in Turkey, the mean ALT value was 32 IU/ and the number of cases with abnormally high ALT values was reported to be 34.8%. The aforementioned study and our data were considered consistent in the sense that patients with mean and abnormally high ALT measurements were in the minority.[23]

We had LDH measurements in 78 patients, and the mean LDH of these patients was 262.70 U/L. In a study conducted in China and including 109 cases, the mean LDH value of brucellosis cases was 288 U/L, close to our data. However, the maximum LDH value in their study was reported as 476.5 U/L, while the maximum value in our study was 874 U/L, which is quite high and confusing.[24]

In addition, the same directional relationship was observed between LDH and ALT elevation due to organ involvement and titer values. Therefore, patients diagnosed with Brucellosis with a high titer should be more careful in terms of complications. It is reported that combined and long-term antibiotic therapy affects the prognosis positively and prevents relapses. Although there is no definitive form of treatment, increasing the duration of treatment to more than six weeks is thought to reduce relapse.[25,26] Despite all studies, it is not clear what the optimal duration of treatment and regimen will be in cases of relapse, chronic brucellosis, complicated brucellosis, and further multicenter studies are needed in these cases. It is thought that regulating the duration of treatment will reduce the morbidity and mortality due to brucellosis.[27] Based on meta-analysis studies, the evaluation found that the risk of developing relapse was lower with six-week antimicrobial treatments compared to four-week regimens. It is recommended to use six-week therapy in patients diagnosed with acute brucellosis. However, the duration of treatment in complicated brucellosis varies.[28,29] In order to prevent the development of complications, studies can be conducted to give more aggressive and prolonged treatment to individuals with high titers and to give shorter treatment to individuals with low titers so that they are not exposed to the side effects of combined antibiotherapy for a long time.

Limitations

Retrospective and small number of cases. Lack of long-term follow-up results.

CONCLUSION

Although fever and then joint pain come to mind when we think of Brucellosis, in our study, joint pain was the first complaint and fever was the third most common complaint. Therefore, individuals presenting with nonspecific complaints should be suspected of having Brucellosis in endemic areas. There is a correlation between the Brucella serum tube agglutination titer and inflammation markers ESR and CRP. It may be necessary to be careful in terms of complications in individuals with high titers and inflammation markers. In fact, treatment duration may be changed in these patients before complications develop.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Yozgat Bozok University Medical Faculty Clinical Researches Ethics Committee (Date: 10.11.2022, Decision No: 2017-KAEK-189_2022.11.10_06).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Altay G. Kültür Pozitif 70 Bruselloz hastasının klinik ve laboratuvar verilerinin değerlendirilmesi & antibiyotik duyarlılıklarının E-test yöntemi ile incelenmesi, Uzmanlık Tezi. Sağlık Bakanlığı Haseki Eğitim ve Araştırma Hastanesi Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, İstanbul, 2008.
2. Shapiro DS, Wong JD. Brucella. Murrey PR, Baron EP, Faller MA, Tenover FC, Yolken RH, eds. Manual of Clinical Microbiology. 7. Edition. American Society for Microbiology: 1999: 625-629.
3. Çiçek Y. Bruselloz tanılı hastaların klinik, laboratuvar ve epidemiyolojik özelliklerinin incelenmesi. 2021. file:///C:/Users/admn/Downloads/bruselloz-tanili-hastalarin-klinik-laboratuvar-ve-epidemiyolo jik-ozelliklerinin-incelenmesi.pdf
4. Bilgehan H. Klinik Mikrobiyolojik Tanı. Fakülteler Kitabevi, Barış Yayınları; İzmir. 1992: 203-207.
5. Bilgehan H. Brucella. Klinik Mikrobiyoloji-Özel Bakteriyoloji ve Bakteri Enfeksiyonları. 10.baskı. Barış Yayınları, Fakülteler Kitabevi; İzmir. 2004: 157-168.
6. Dabanlıoğlu B. Erzincan ili ve yöresinde bruselloz seroprevalansı ve seropozitif olguların klinik bulgularla ilişkisi. Doktora Tezi, Erciyes Üniversitesi Sağlık Bilimleri Enstitüsü, Kayseri, 2005.
7. Ulug M, Can-Ulug N. Brusellozlu 78 olgunun degerlendirilmesi/ evaluation of 78 cases with brucellosis. *Klimik Derg*. 2010;23(3):89.
8. Aydın FE. Süt ve süt ürünlerinde *Brucella* cinsi bakterilerin araştırılması, Yüksek Lisans Tezi, Mersin Üniversitesi Sağlık Bilimleri Enstitüsü Tıbbi Mikrobiyoloji Anabilim Dalı, Mersin, 2007.
9. Selçuk K. Bruselloz ve tedavi sorunu. *İnfeksiyon Derg* (*Turk J Infect*). 2006;20(3):227-230.
10. Rubinstein E, Lang R, Shasha B, et al. Invitro susceptibility of *Brucella melitensis* to antibiotics. *Antimicrob Agents Chemother*. 1991;35(9):1925-1927.
11. Akpınar O. Historical perspective of brucellosis: a microbiological and epidemiological overview. *Le Infezioni in Medicina*. 2016;24(1):77-86.
12. Topçu AV, Söyletir G, Doğanay M, Sözen TH. Bruselloz. In: İnfeksiyon Hastalıkları. Ankara Nobel Tıp Kitabevi: 1996: 476-491.
13. Türkçapar N, Kurt H. Bruselloz. İçinde: Kurt H, Gündeş S, Geyik MF, eds. Enfeksiyon Hastalıkları. Nobel Tıp Kitabevi. 2004:7:54-61.
14. Büke Ç, Çiçeklioğlu M, Türk M, Atalay S, Tuncel M. Ovakent beldesinde bruselloz seroprevalansı ile hastalık konusundaki bilgi ve davranışın saptanması. *İnfeksiyon Derg*. 2006;20(1):23-26.
15. Köse Ş, Senger SS, Akkoçlu G, et al. Clinical manifestations, complications, and treatment of brucellosis: evaluation of 72 cases. *Turk J Med Sci.* 2014;44(2):220-223. doi:10.3906/sag-1112-34
16. Tohme A, Zein E, El Rassi B, Koussa S, Nasnas R. Human brucellosis in Lebanon. clinical features and therapeutic responses in 88 patients. *J Med Liban*. 2004;52(3):149-155.
17. Saçar S, Hırçın-Cenger D, Toprak S, Demir M, Turgut, H. Otuz bruselloz olgusunun klinik değerlendirilmesi. *İnfeksiyon Derg*. 2008;22(1):11-14.
18. Arapović J, Špičić S, Ostojić M, et al. Epidemiological, clinical and molecular characterization of human brucellosis in Bosnia and Herzegovina-an ongoing brucellosis outbreak. *Acta Medica Academica*. 2018;47(1):50-60.
19. Şahin M, Cesur S, Enki S. Endemik olduğu bir bölgeden 83 olgu ile brusella enfeksiyonu. *Ortadoğu Tıp Derg.* 2019;11(2):101-106.
20. Demir T. Seroprevalence of brusellosis in Kırşehir province and significance of serological and biochemical tests in the diagnosis of brucellosis. *Selçuk Med J.* 2012;28(3):173-177.
21. Kalkan A, Felek S, Akbulut A, Papila Ç, Demirağ K, Kılıç SS. Bruselloz için risk taşıyan kişilerde mesleklerinde çalışma süresinin bruselloz seropozitifliği ve aglütinasyon titresi üzerine etkisi. *Flora*. 1998;3(2):107-112.
22. Yardımcı C, Sarı ND, Ceylan B, Ulutürk R, Fincancı M. Brusellozlu olgularda semptomların süresi ile standart tüp aglütinasyon titreleri, kan kültürlerinde üreme ve lokomotor sistem tutulumu arası ilişkinin irdelenmesi. *Göztepe Tıp Derg.* 2009;24(2):69-72.
23. Kazak E, Akalın H, Yılmaz E, et al. Brucellosis: a retrospective evaluation of 164 cases. *Singapore Med J.* 2016;57(11):624-629. doi:10.11622/smedj.2015163
24. Shi C, Wang L, Lv D, et al. Epidemiological, clinical and laboratory characteristics of patients with *Brucella* infection in Anhui province, China. *Infect Drug Resist*. 2021;14:2741-2752. doi:10. 2147/IDR.S319595

25. Pappas G, Seitaridis S, Akritidis N, Tsianos E. Treatment of brucella spondylitis: lessons from an impossible meta-analyses and initial report of efficacy of a fluoroquinolone-containing regimen. *Int J Antimicrob Agents.* 2004;24(5):502-507.
26. Kizilkilic O, Turunc T, Yildirim T, Demiroglu YZ, Hurcan C, Uncu H. Successful medical treatment of intracranial abscess caused by Brucella spp. *J Infect.* 2005;51(1):77-80.
27. Kaya S. Bruselloz ve tedavi sorunu. *İnfeksiyon Derg.* 2006;20(3):227-230.
28. Montejo JM, Alberola I, Glez-Zarate P, et al. Open, randomized therapeutic trial of six antimicrobial regimens in the treatment of human brucellosis. *Clin Infect Dis.* 1993;16(5):671-676.
29. Yavuz SŞ, Xu C, Benli A, et al. The Turkish clinical microbiology and infectious diseases society (KLİMİK) evidence-based guideline for the diagnosis and treatment of Brucellosis, 2023. *Klimik Derg.* 2003;36(2):86-123.